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Deletion-Type Allele of the Angiotensin-Converting Enzyme Gene Is Associated With Progressive Ventricular Dilation After Anterior Myocardial Infarction

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Objectives. **This study sought to determine whether patients who are homozygous for the deletion (D)-type allele of the angiotensin-converting enzyme gene display augmented ventricular dilation after myocardial infarction.**

Background. **Recent evidence suggests that the deletion-type allele of the angiotensin-converting enzyme gene (DD genotype) is associated with an increased prevalence of myocardial infarction and myocardial hypertrophy. However, it is unknown whether the DD genotype is associated with adverse cardiac remodeling. To address this question we determined the genotype in patients enrolled in the Captopril and Thrombolysis Study (CATS), a prospective trial in which patients received either captopril or placebo during and after thrombolysis for a first anterior myocardial infarction.**

Methods. **Cardiac volume was determined by echocardiography immediately after thrombolysis and at 1-year follow-up. The genotype for the angiotensin-converting enzyme was determined in 96 patients. Norepinephrine levels were assessed during and immediately after thrombolysis.**

Results. **Immediately after thrombolysis, cardiac volume did not differ between genotype groups. However, at 1-year follow-up, both end-systolic and end-diastolic left ventricular volumes were significantly greater in the DD-genotype group. Norepinephrine increased to higher levels in the DD-genotype group that received placebo therapy. Captopril treatment effectively blunted both the norepinephrine increase and cardiac dilation in the DD-genotype group.**

Conclusions. **This exploratory study suggests that homozygosity for the angiotensin-converting enzyme deletion-type allele is associated with augmented neurohumoral activation as well as augmented cardiac dilation after an acute anterior myocardial infarction, an effect that may be susceptible to angiotensin-converting enzyme inhibition.**

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The activity of the angiotensin-converting enzyme may be an important modulator of cardiac growth and remodeling. In particular, recent findings (1,2) suggest that angiotensin-converting enzyme activity and messenger ribonucleic acid expression are induced after myocardial infarction and during cardiac pressure overload. Furthermore, inhibition of angiotensin-converting enzyme reduces ventricular dilation after myocardial infarction (3).

Genetic background may contribute to the activity of angiotensin-converting enzyme. An insertion/deletion polymorphism in the human angiotensin-converting enzyme gene has been described in which subjects who are homozygous for the deletion allele (DD genotype) have higher levels of angiotensin-converting enzyme activity. Furthermore, the DD genotype has been associated with an increased prevalence of myocardial infarction (4), left ventricular hypertrophy (5) and hypertrophic cardiomyopathy (6).

However, it is not presently known whether the DD genotype is associated with augmented cardiac dilation after myocardial infarction. We tested this hypothesis in patients enrolled in the Captopril and Thrombolysis Study (CATS) (7), a multicenter prospective clinical trial that investigated the effect of captopril versus placebo in patients after a first anterior myocardial infarction.

Methods

The CATS trial (7) is a double-blind, randomized, placebo-controlled study in patients with a first anterior myocardial infarction, treated with thrombolytic therapy (streptokinase intravenously). Two hundred ninety-eight patients were enrolled in 10 hospitals in The Netherlands and were randomized to receive either captopril (target dose 75 mg/day) or placebo. Immediately after completion of the streptokinase infusion, treatment was started and continued for 1 year. The primary objective of the trial was to assess the long-term effect of captopril on echocardiographic left ventricular volume. Echocardiographic determination of cardiac end-systolic and end-

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Table 1. Volume Indexes (ml/m^2) in Three Separate Genotype Groups

	II-Genotype Group (n = 20)	ID-Genotype Group (n = 42)	DD-Genotype Group (n = 34)
End-systolic index			
Baseline	23.9 ± 4.4	23.5 ± 1.2	24.1 ± 1.5
After 1 yr	24.2 ± 2.4	25.8 ± 1.7	30.2 ± 3.1
End-diastolic index			
Baseline	54.9 ± 2.8	52.9 ± 2.1	53.1 ± 2.2
After 1 yr	54.9 ± 3.4	59.2 ± 2.3	62.3 ± 3.7

Analysis of variance with contrast demonstrated a significant linearity of the effect of the deletion allele on systolic volume after 1 year ($p = 0.007$) and on diastolic volume after 1 year ($p = 0.013$). Data presented are mean value ± SEM. DD = genotype of homozygosity for the angiotensin-converting enzyme deletion allele; ID = genotype of one angiotensin-converting enzyme deletion allele and one angiotensin-converting enzyme insertion allele; II = genotype of homozygosity for the angiotensin-converting enzyme insertion allele.

diastolic volumes was performed in the apical four- and two-chamber views. Recordings were made directly after thrombolysis and 1 year after myocardial infarction.

Blood samples were taken to determine the time course of alpha-hydroxybutyrate dehydrogenase release as a measure of infarct size according to a standard protocol. In addition, blood samples for determination of norepinephrine levels and angiotensin-converting enzyme activity were measured at baseline (before thrombolysis) and 1, 12 and 24 h after thrombolysis.

In 96 patients, the genotype for the angiotensin-converting enzyme was determined after completion of echocardiographic follow-up by a method previously described in detail (5). All patients enrolled in the trial were asked to visit the clinic to have a blood sample taken for genotyping. The laboratory responsible for genotyping performed the determinations without knowledge of any clinical data.

Statistical analysis. Patients were grouped with regard to genotype. Data for ventricular volumes are depicted in Table 1 for each group. Because heterozygous patients did not significantly differ from patients homozygous with respect to the insertion allele, data from these groups were pooled for analysis.

Group differences were tested by analysis of variance in which echocardiographic volume data were corrected for infarct size by adding the cumulative alpha-hydroxybutyrate dehydrogenase as a covariate. Baseline characteristics of the patients in which the genotype was determined were comparable to the overall study population.

Results

Baseline characteristics did not differ significantly between DD-genotype and non–DD-genotype groups, including enzymatic infarct size and left ventricular volume (Table 2). A total of 45 patients received captopril (17 with the DD-genotype), and 51 received placebo (17 with the DD genotype).

At 1-year follow-up, both end-systolic and end-diastolic volume indexes were significantly higher in the DD-genotype group (Fig. 1). Left ventricular volumes were intermediate in the heterozygous group (Table 1). Analysis of variance with contrast revealed linear effects of the deletion allele for both systolic ($p = 0.007$) and diastolic volumes ($p = 0.013$) after 1 year.

When the groups were subdivided by placebo or captopril treatment, only the placebo-treated DD-genotype group displayed a significant increase in left ventricular end-systolic volume index; the increase in systolic volume in the captopril-treated DD-genotype group was not statistically significant (Table 3).

The surge of norepinephrine levels after thrombolysis was similar or somewhat lower in the DD-genotype group than in the non–DD-genotype group (norepinephrine 1 h after thrombolysis [mean ± SD] 797 ± 71 pg/ml in the DI/II genotype group vs. 595 ± 85 pg/ml in the DD-genotype group, p = NS). However, when the groups were subdivided by treatment, a different pattern was observed. In the DD-genotype group treated with placebo, the surge in norepinephrine was increased compared with that in the placebo-treated non–DD-genotype group (Fig. 2). In contrast, in the DD-genotype group who received captopril, the surge in norepinephrine levels was not significantly decreased compared with that in the captopril-treated non–DD-genotype group (norepinephrine 1 h after thrombolysis, 779 ± 181 pg/ml in the DD genotype group vs. 1,054 ± 175 pg/ml in the DI/II-genotype group, p = NS).

Finally, baseline angiotensin-converting enzyme activity was higher in the DD-genotype group (29 ± 3 vs. 23 ± 2 U/liter, $p = 0.04$).

Discussion

The present exploratory study suggests that ventricular dilation after anterior myocardial infarction is augmented in patients who are homozygous for the deletion-type allele of the angiotensin-converting enzyme gene. This seems to be sensitive to angiotensin-converting enzyme inhibition. Our study showed that the increase in ventricular volume was significant in the DD-genotype group treated with placebo but was no longer significant in those who received capto-

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Table 2. Baseline Characteristics in Patients Homozygous for the Angiotensin-Converting Enzyme Deletion Alleles and in Patients With Genotypes Not Homozygous for Angiotensin-Converting Enzyme Deletion Alleles

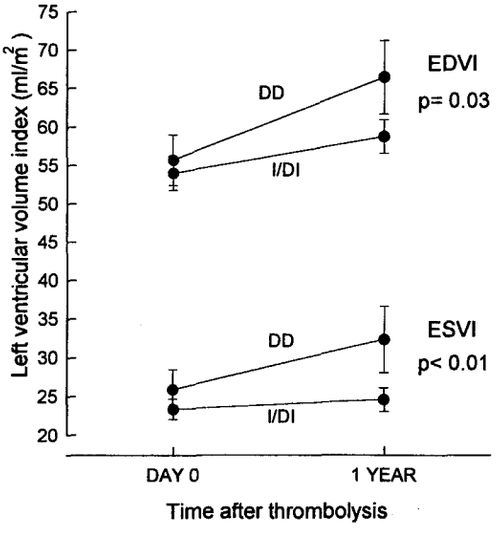
	ID/II-Genotype Group (n = 62)	DD-Genotype Group (n = 34)
Mean age (yr)	59.1 ± 9	58.3 ± 9
Gender (M/F) (%)	82/18	85/15
Clinical history (%)		
Ischemic heart disease	8	3
Hypertension	23	21
Diabetes mellitus	5	15
Current smoker	63	73
Killip class (%)		
I	81	76
II	18	24
Concomitant medication at randomization (%)		
Beta-blockers	23	24
Calcium-antagonists	15	9
Diuretic drugs	10	3
Nitrates	15	9
Systolic blood pressure (mm Hg)	127 ± 2	125 ± 3
Diastolic blood pressure (mm Hg)	75 ± 1	77 ± 2
Total alpha-HBD	1,277 ± 122	986 ± 136
End-systolic volume (ml/m^2)	23.6 ± 1.1	24.1 ± 1.5
End-diastolic volume (ml/m^2)	53.7 ± 1.7	53.1 ± 2.2

Data presented are mean value ± SEM or number of patients. F = female; HBD = hydroxybutyrate dehydrogenase; M = male; other abbreviations as in Table 1.

pril. The results cannot be explained by differences in infarct size because infarct size (as determined by total alpha-hydroxybutyrate dehydrogenase) was similar to or even smaller than that in the DD-genotype group.

The mechanisms responsible for these findings cannot be directly derived from our data. However, neurohumoral factors may be different in patients of the various angiotensin-converting enzyme genotype groups. First, plasma angiotensin-converting enzyme activity may be increased in patients with the DD genotype, as has been previously described (8). The response to inhibition of the enzyme also seems to be altered in patients with the DD genotype: The normally occurring increase in angiotensin-converting enzyme activity during angiotensin-converting enzyme inhibition (*upregulation*) (9) seems to be enhanced in patients with the DD genotype (10).

Figure 1. End-systolic volume index (ESVI) and end-diastolic volume index (EDVI) in ml/m^2 measured by echocardiography at baseline (after thrombolysis) and after 1 year. Both treatment groups are pooled. Results are mean value ± SEM, and p values for the differences at 1 year between the DD-genotype and II/DI-genotype groups are indicated, as obtained by analysis of variance.



The present data suggest that the norepinephrine surge on reperfusion was significantly higher in untreated patients with the DD genotype. This elevation was susceptible to angiotensin-converting enzyme inhibition because it did not occur in the DD-genotype group treated with captopril. Thus, neurohormonal activation after myocardial infarction may be amplified in patients with the DD genotype, thereby possibly leading to an adverse outcome.

Other potential mechanisms should be considered as well, such as differences in blood pressure or patency of the reperfused arteries. The latter is suggested by the finding that the DD genotype is also associated with an increased prevalence of restenosis after coronary angioplasty during acute myocardial infarction (11). With regard to blood pressure, it is known that the DD genotype is not associated with hypertension (12), and we also found no differences in blood pressure. However, this finding does not preclude changes in blood pressure that may occur in these patients without leading to classic hypertension.

Table 3. Volume Indexes As Subdivided by Genotype and Treatment

Treatment	End-Systolic Volume Index (mean change ml/m² ± SEM)		End-Diastolic Volume Index (mean change ml/m² ± SEM)	
	ID/II-Genotype Group (n = 39)	DD-Genotype Group (n = 18)	ID/II-Genotype Group (n = 39)	DD-Genotype Group (n = 18)
Placebo (n = 28)	1.5 ± 2.1	7.1 ± 3*	2.9 ± 3.4	7.6 ± 4.9
Captopril (n = 29)	2.3 ± 2	3.1 ± 3	4.5 ± 3.3	6.7 ± 4.9

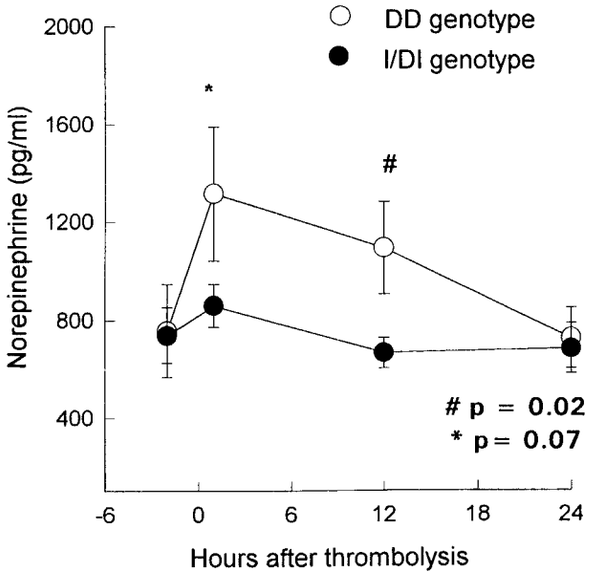
*$p < 0.05$, significant increase from baseline (95% confidence interval 0.2 to 14). Abbreviations as in Table 1.

Finally, we found that the effect of the angiotensin-converting enzyme insertion/deletion polymorphism on ventricular volumes after myocardial infarction is proportional to the number of deletion alleles present (either one or two). Such additive effects, rather than an all-or-nothing phenomenon, further suggest that this gene may serve as a disease modifier rather than as a direct causal agent.

Study limitations. The present study was not designed to establish a causal role for a specific gene in postinfarction remodeling. Any association between a specific polymorphism and a particular phenotype may not be attributable to the gene under investigation but rather to the region of the genome on which the gene is located. Further studies will be needed before the angiotensin-converting enzyme gene can be linked to dilation of the left ventricle after myocardial infarction.

Furthermore, we studied a small number of patients and, in particular, small treatment groups. Therefore, it should be emphasized that the results need further confirmation in larger studies.

Figure 2. Plasma norepinephrine (pg/ml) as determined in samples taken before (first point) and after thrombolysis starting 1 h after thrombolysis. Only placebo-treated patients are depicted. Results are mean value ± SEM, and p values are obtained by analysis of variance.



Clinical implications. The present data suggest that in the future genetic markers may be of value in stratifying patients according to risk of developing ventricular dilation. The finding that augmented left ventricular dilation and increased norepinephrine levels were blunted by captopril therapy suggests a role for the angiotensin-converting enzyme gene in this process. Therefore, our study is in line with investigations that demonstrated the beneficial effects of angiotensin-converting enzyme inhibition on cardiac remodeling after myocardial infarction (3). However, our limited sample size does not allow us to draw conclusions with respect to the possible additional benefit that angiotensin-converting enzyme inhibition may have in patients with the DD genotype.

Conclusions. Taken together, our data suggest that homozygosity for the angiotensin-converting enzyme deletion-type allele renders patients more susceptible for neurohumoral activation after an anterior myocardial infarction, which in turn may augment left ventricular dilation.

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